Citizen Petition - Label Gluten in Drugs

As of 7/24/16, the FDA is considering and the Comment period remains open for the Citizen Petition, FDA Docket Item FDA-2015-P-5081, at https://www.regulations.gov/document?D=FDA-2015-P-5081-0001.

This is a citizens' petition by O'Hara, Vogel, Bazlen, Craig, Denning, Willson, Weir and Larock that asks the FDA to require "that medications disclose when gluten is present in excess of 20 ppm gluten and/or when medications do not meet the conditions of the finalized (currently proposed) FDA rule, 'Gluten-Free Labeling of Fermented or Hydrolyzed Foods'."

In the past, the FDA has taken citizens' needs seriously in similar matters. So yes, your comment can make the difference! If the form asks who you represent, you can type in "Individual Consumer" if you are not a representative of an interested organization. Individuals can be anonymous; their contact information does not have to be listed on the internet.

Background:

Celiac Support Group's all-volunteer board spent much of 2015 discussing how lack of regulation of gluten in medications affects celiacs. The FDA declined to regulate this in May. In November, the FDA proposed an action relating only to gluten-free-labeled food products. After reviewing these and the history and scope of "gluten in medications" issues, the board members, as individual citizens, filed the citizens' petition to propose a solution that would "protect celiacs and increase their ability to maximize their quality of life without imposing burdens on medication manufacturers or the FDA."

The next paragraph is a nutshell of what it's all about, followed by a section summary and the full petition.

Medications (both prescription and over-the-counter) are not covered by the FDA's final rule for gluten-free labeling of foods and dietary supplements. More than 3 million USA citizen celiacs, plus those with other gluten-related disorders, consume many medications among the more than 10,000 prescription medications and more than 300,000 over-the-counter medications available. Those medications that voluntary disclose whether they do or do not contain gluten is unacceptably small. Medication manufacturers' responses to concerned (and sometimes sickened) patients' questions appear to reflect manufacturers' uncertainties about gluten in their products. Taking the FDA at its word that the overall risk of gluten in medications is small and understanding the FDA's and medication manufacturers' wish to avoid "excessive labeling," the citizens' petition suggested solution is to require labeling a medication only if more than 20 ppm gluten is present. The exact request is for "A regulation in the form of a mandatory rule: that medications disclose when gluten is present in excess of 20 ppm gluten and/or when medications do not meet the conditions of the finalized (currently proposed) FDA rule 'Gluten-Free Labeling of Fermented or Hydrolyzed Foods'."

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I. People with celiac disease are experiencing problems with prescriptions and over-the- counter medications that are not resolved by the risk analysis in the FDA’s letter.

II. The proposed rule supports celiac disease patients’ rights as intended by the Americans with Disabilities Act.

III. The current situation creates stress for celiac individuals whenever they are prescribed medications, whenever their medications are changed, and whenever they experience side effects from their medications. Such stress is not conducive to health.

IV. Given the current situation, the FDA’s risk analysis in its 5/12/2015 letter and its plan to provide guidance to manufacturers are inadequate to relieve celiacs of concern or to protect them from actual danger, because the problem is not with the overall gluten risk in medications but rather with the uncertainty present regarding every individual drug product.

V. The FDA’s current stated intention to offer guidance to drug manufacturers increases rather than reduces uncertainties about gluten in medications.

VI. When problems arise, it is unfair to place the burden of resolving them on concerned individual celiacs and pharmacists.

VII. The requested mandatory rule proposed above would reduce manufacturer uncertainties and promote standardization.

VIII. The good news in the FDA's 5/12/2015 letter is that its risk analysis indicates that violations of the requested proposed rule are expected to be rare. The better news is that, in the rare instances in which violations of the requested proposed mandatory rule might occur, celiac consumers would have a remedy.

IX. An advantage of the requested proposed mandatory rule above over FDA guidelines is that it provides a single, measurable standard for those creating ingestible products worldwide that are considered gluten free.

X. An advantage of the requested proposed rule over FDA guidance is that any allegations or disputes involving gluten in medications would be resolved by a single testable standard, rather than by requiring investigation of anecdotal reports.

XI. In addition to differences in gluten concentration between a single serving of an oral medication and a single serving in a 30 gram cookie labeled gluten free, both containing the same amount of gluten, other differences between these "equal gluten amount" medication and cookie affect celiacs.

Opposition to the requested proposed mandatory rule.

XII. We could find no written statements by the pharmaceutical or over-thecounter medications industries opposing the labeling of gluten above 20 ppm in drug products. Written statements by medication manufacturers in responses to FDA Docket 2011-N- 0842 appear to support or be neutral regarding the proposed rule.

XIII. Because the proposed rule does not require manufacturers to remove all gluten from medications and in addition does not require pharmaceutical companies to be explicit about their excipients, and because the proposed rule would not result in excessive labeling, the proposed rule should not cause manufacturers or the FDA to object on these grounds.

Conclusion

C. Environmental Impact

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Citizen Petition to Commissioner of Foods and Drugs

(accepted as Docket Item FDA-2015-P-5081-0001)

Date: December 13, 2015

The undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act (including Sections 501 and 502) and/or the Public Health Service Act and/or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs, to request the Commissioner of Food and Drugs to issue a regulation.

A. Action Requested

There being no existing regulation, proposed regulation, order, or proposed order on this subject, the undersigned propose the following: A regulation in the form of a mandatory rule: that medications disclose when gluten is present in excess of 20 ppm gluten and/or when medications do not meet the conditions of the finalized (currently proposed) FDA rule “Gluten-Free Labeling of Fermented or Hydrolyzed Foods”. For this purpose, gluten is defined as any gluten grain or any gluten-grain product derivative, whether or not processed to remove gluten.

B. Statement of Grounds

Note that the requested proposed mandatory rule does not ban either the use or incidental presence of gluten in medications, these being the issues primarily raised by prior petitions and rulings. Its advantages and anticipated objections are enumerated below.

Regulatory Background:

In 2008, Mr. Michael Weber petitioned the FDA regarding the presence of gluten in drug products. Mr. Weber asked for gluten to be excluded from allowed excipients or that there be a labeling rule.

On 12/21/2011, the FDA opened FDA Docket 2011-N-0842 to address the need to “help individuals with celiac disease avoid the presence of gluten in drug products.” Under *Approaches*, the docket stated: “If interested stakeholders do not identify reasons why certain ingredients must be derived from wheat, barley, or rye—or why the flexibility to use these grains as ingredient sources is important— discontinuing use of such ingredients may be attractive for its simplicity and effectiveness in addressing the issue.” When asking for information and comments, the Docket specifically asked about “Current Practice,” “Flexibility and Consequences,” “Exposure Estimate,” “Routes of Administration,” and “Incidental Addition of Gluten.” This list suggested that the FDA was asking to hear from pharmaceutical companies rather than the celiac public. When the comment period closed on 3/10/2012, the docket had only 73 responses.

Several of these, however, were from groups who represented large numbers of medical practitioners and and large numbers of celiacs, and their comments supported the need for regulation.

On 8/5/2014, the FDA’s Final Rule for companies to voluntarily label food products as gluten free went into effect. This Final Rule specifically excluded medications. The Final Rule states that food products voluntarily labeled gluten free will not contain, as an ingredient, any gluten grain, any gluten-grain product derivative not processed to remove gluten (like flour), or any gluten-grain product derivative processed to remove gluten (like wheat starch) if its presence results in 20 or more ppm gluten in the final product.

On 3/16/2015, the consumer group Public Citizen filed a lawsuit against the FDA on behalf of Mr. Michael Weber. Public Citizen asked the FDA to respond to Mr. Weber’s 2008 citizen’s petition.

On 5/12/2015, the FDA issued a letter to Mr. Michael Weber in response to the lawsuit. This letter, titled “Citizen Petition Partial Approval and Denial Response Letter from FDA CDER to Mr Michael Weber Redacted,” may be accessed at http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0333-0030 (all links in this document were accessed in October through December 2015). The FDA wrote, “Your labeling request is granted in that we affirm our pre- existing expectation that any drug product containing wheat gluten as an inactive ingredient should be labeled to indicate its presence.” However, the FDA declined to further regulate regarding gluten in drug products, based on information provided in the 2008 petition and FDA Docket 2011-N-0842 plus an FDA risk analysis. Instead of regulating, the FDA wrote, “We intend to issue draft guidance for industry regarding gluten in drug products and associated labeling.”

The FDA letter acknowledged that uncertainty exists with respect to gluten in medications. The letter also acknowledged that gluten may be present in a medication from a gluten grain (wheat, rye, barley), gluten grain crossbred hybrid or gluten grain derivative, as follows: “Gluten could be introduced into a drug product through the following pathways: • As an inactive ingredient, directly and intentionally added (see above); • As an impurity in an ingredient derived from wheat, e.g., present at low levels in wheat starch, modified starch, or other starch-derived ingredients, serving no purpose in the ingredient or in the drug product; • As an impurity in certain ingredients produced by fermentation; or • As an adventitious contaminant, present in a drug product because the drug product or one or more of its ingredients unintentionally came into contact with gluten during processing, storage, or transportation.”

In its letter, the FDA noted that “A 30-gram serving of food, corresponding to a single cookie for example, could contain up to 0.6 mg gluten” and still be labeled gluten free. The FDA’s risk analysis at several points references this amount.

On 9/29/2015, The Gluten in Medicine Disclosure Act of 2015 was introduced in the House of Representatives and is currently in the Committee on Energy & Commerce. The bill, if eventually enacted as written, would “amend the Federal Food, Drug, and Cosmetic Act to require the label of drugs intended for human use to contain a parenthetical statement identifying the source of any ingredient constituting or derived from a grain or starchcontaining ingredient.” (link: https://www.govtrack.us/congress/bills/114/hr3648).

The proposed bill indicates the high level of concern regarding gluten in medications. It differs from the requested proposed mandatory rule in that it requires labeling when any ingredient is or is derived from a grain or starch-containing ingredient. The requested proposed mandatory rule does not require labeling unless gluten is present in a medication, whether as part or all of one or more ingredients or from cross-contamination, at levels above 20ppm gluten.

On 11/17/15, the FDA released a proposed rule, “Gluten-Free Labeling of Fermented or Hydrolyzed Foods”: According to the FDA, “The proposed rule, when finalized, would require [food] manufacturers to make and keep records demonstrating assurance that: the food meets the requirements of the gluten-free food labeling final rule prior to fermentation or hydrolysis, and the manufacturer has adequately evaluated its process for any potential gluten crosscontact, and where a potential for gluten cross-contact has been identified, the manufacturer has implemented measures to prevent the introduction of gluten into the food during the manufacturing process.” (See http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm472778.htm).

Additional relevant information

The following additional information was not considered in the FDA’s 5/12/2015 letter. This additional information supports the need for and desirability of the requested proposed rule.

In 2001, J P Crowe (Pharm.D.) and N P Falini (M.A., R.D.) published the results of their survey on “Gluten in pharmaceutical products” in the American Journal of Health-System Pharmacy (2001 Mar 1;58(5):396-401) (accessed at http://www.drofrx.com/Notes_files/Gluten%20in%20pharmaceutical%20products.pdf). The 6-item survey was sent to 172 “pharmaceutical companies listed in the 1998 Physicians’ Desk Reference16 and the 1998 generics supplement to Pharmacy Times.” Ultimately, 100 companies responded.

The study notes: “Optimal care of the celiac disease patient requires that the pharmacist and other members of the health care team have accurate information about the gluten content of pharmaceutical and nutritional products. The objective of this study was to identify pharmaceutical companies with an established policy of producing only gluten-free products and to identify specific gluten-free and gluten-containing products produced by companies without such a policy.”

The study adds: “The information obtained from this survey, although somewhat dated, highlights the challenges in obtaining gluten-free drug and nutritional products. Few companies reported definitively that their products were gluten free. Raw materials obtained from outside sources were the primary reason for this ambiguity.”

The study authors observed that “Procuring gluten-free products is facilitated when a pharmaceutical company has an established policy of producing only gluten-free products. In such a case, much of the uncertainty about the appropriateness of a product for the celiac disease patient is removed. Only five of the companies surveyed had such a policy, however. Further complicating the picture is that information is only as current as the date on which it was communicated. Consequently, the patient, the pharmacist, or the physician must contact a manufacturer periodically to be sure that a given product’s status has not changed. It is best to refer to the lot number of the product whenever possible.”

In the survey, “a significant number of respondents were not aware of excipients other than wheat starch that may contain gluten.”

The survey concluded, “Only 5 of 100 pharmaceutical companies that responded to a survey reported having a policy of producing gluten-free products. Many companies believed their products to be gluten free but could not guarantee it.”

Important Aspects of the situation in 2001 remain unchanged to the present.

As far as the undersigned are aware, this survey has not been repeated. However, several factors, outlined in sections A through C below, indicate that the situation reported in 2001 has not improved.

A. Drug companies continue to be unsure about the gluten status of their products.

Drug “company representatives are very helpful and knowledgeable about gluten, but while some companies say ‘all of our medications are gluten free,’ it is more common to hear a version that ‘none of the ingredients in the medication contain gluten, but we do not test for it and cannot guarantee against cross contamination,’ or worse, ‘although the filler ingredients “shouldn’t” contain gluten they are purchased from outside sources and not tested for gluten.’ [One] representative [has] added something new—’people who have celiac disease should contact their doctor before taking this medicine.’” (From Celiac Support Group blog post, “Gluten In Drugs II: How to Find Out If Your Medications Are Gluten Free” 3/1/15, at http://www.celiacsupportgroup.org/celiac-support-group-blog/gluten-in-drugs-ii-how-to-findout-if-your-medications-are-gluten-free)

B. Other than calling drug companies, celiac patients have few alternative ways to determine what drug companies say about the gluten status of their medications.

The few companies who declare that their products either are gluten free or contain gluten are listed at a website, http://glutenfreedrugs.com. The GlutenFreeDrugs website is maintained as an unpaid service by Steve Plogsted, Pharm.D., and the dates for information provided are not included.

A patient also can check prescription product package inserts (available at http://www.druginfonet.com/ and prescription drug ingredient information via http://pillbox.nlm.nih.gov/pillimage/search.php.

We recently compared 9 drugs listed at http://glutenfreedrugs.com as containing gluten with the information for those drugs recorded at http://pillbox.nlm.nih.gov/pillimage/search.php. Our results were:

Item Selected (nonrandom)	Description at glutenfreedrugs	Ingredient(s) at pillbox	Result
1	Contains gluten	(not listed)	No longer made?
Item Selected Description at Ingredient(s) at Result (nonrandom) glutenfreedrugs pillbox			
2	May contain gluten	(not listed)	Over-the-counter drug
3	Contains gluten	(not listed)	No longer made?
4	Weak gluten content	Wheat gluten	Agree
5	Contains wheat	Starch, wheat	Agree
6	Contains no starch but company will verify that is GF	(no starch is listed)	Agree
7	Contains no starch but company will not verify that is GF	Starch, wheat	Difference
8	Outer coating could be from wheat source	(possibility not mentioned)	Difference
9	NOT GF	Inactive ingredients listing says: N/A	Difference

What we found was that some of the information at glutenfreedrugs may be out of date, and in any case this website's information does not always agree with what appears at the pillbox site.

C. Researchers continue to mention drug excipients as a possible source of "hidden glutens" for celiacs.

A recent "State of Art" clinical review article on "Celiac disease and non-celiac gluten sensitivity", published in October 2015 in BMJ, includes "Drug fillers (prescription and over the counter items, including dietary supplements)" among other possible "hidden glutens" that may negatively affect people with celiac disease. (See: BMJ 2015; 351 doi: http://dx.doi.org/10.1136/bmj.h4347 [Published 05 October 2015] and cited as: BMJ2015;351:h4347)

Several other factors have changed since 2001 which are of concern to celiacs, as outlined in sections D through K below:

D. Advances in testing procedures reveal that the gluten content of gluten grains and derivatives can vary widely.

Drug companies have good reason to be vague about the gluten status of their products when they are unsure. It is becoming clearer that the gluten content of gluten grains and derivatives can vary, for example:

"A recent study found wheat starch to contain from less than 5 parts per million of gluten to over 10,000 parts per million of gluten" (at https://www.glutenfreewatchdog.org/news/using-wheat-starch-in-gluten-free-foods/, citing Proceedings of the 27th Meeting Working Group on Prolamin Analysis and Toxicity. Analytical Research Reports. Katharina Konitzer, Herbert Wieser, Peter Koehler. German Research Centre for Food Chemistry, Leibniz Institute, Freising, Germany. Quantitation of gluten in wheat starch by gel permeation chromatography with fluorescence detection Available at: http://www.wgpat.com/proceeding_27th.html).

E. Drug product use has increased since 2001.

By 2013, Mayo Clinic and Olmsted Medical Center researchers reported that "Nearly 70 percent of Americans are on at least one prescription drug, and more than half take two." (http://newsnetwork.mayoclinic.org/discussion/nearly-7-in-10-americans-take-prescriptiondrugs-mayo-clinic-olmsted-medical-center-find/)

The Kaiser Family Foundation reports that in the year 2014 in the USA, the "Total Number of Retail Prescription Drugs Filled at Pharmacies" was "4,002,661,750". (http://kff.org/other/state-indicator/total-retail-rx-drugs/)

F. The number of drugs on the market has increased. and the percentage of them where the issue of gluten has been addressed at glutenfreedrugs is unacceptably small.

Today, the FDA reports, "there are over 300,000 marketed OTC drug products." (http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/over-the-counterdrugs/default.htm)

According to the pillbox website at http://pillbox.nlm.nih.gov/faq.html, "As of March 2014 Pillbox contains 5,364 pill images. These images cover about half of the prescription medications available in the United States."

It appears that there are fewer than 2000 prescription and over-the-counter drug products listed at the glutenfreedrugs website in October 2015 (but we did not count them).

We did not analyze how many of the drugs listed at glutefreedrugs are for prescription medications and how many are for over-the-counter medications, but it is clear that, whether one considers the categories separately or together, and

whether or not outdated information is included on the glutenfreedrugs site, the percentage of drugs that manufacturers voluntarily represent at this website as being either free of gluten or containing gluten is unacceptably small.

G. Suppliers to pharmacies may switch from one generic product to another without advance notice.

Although we cannot document a research study on how often suppliers to pharmacies switch from one generic product to another without advance notice, it appears that this phenomenon is widespread.

H. Drug product excipients are provided by companies located in all parts of the world.

According to the FDA, "Some drugs approved in our nation are either fully manufactured overseas, or made in the United States but have some foreign ingredients. The amount of foreign-made drug products in the United States is rapidly increasing. In 2009, imports regulated by FDA doubled since 2004." (http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194989.htm)

[No capital letter "I" is used in this section, to avoid confusion with Roman numeral "I" in the section below].

J. New evidence reveals that even small amounts of gluten can harm celiacs.

In 2008, according to University of Chicago Celiac Disease Center information (accessed at http://www.cureceliacdisease.org/wp-content/uploads/2011/09/SU08CeliacCtr_v3final.pdf [link has been removed sometime between 12/15/15 and 7/24/16]), "About 10% of patients diagnosed with celiac disease do not get better on a gluten-free diet. This can be due to many different reasons. The most common is dietary indiscretion (unintentional or intentional), because gluten is present in so many foods and medications."

In 2013, the American College of Gastroenterology, in its Clinical Guideline, noted that "In adults, the intestine will often fail to heal despite negative serology and absence of symptoms. This lack of healing may increase the risk of lymphoma, bone disease and ultimately the development of refractory CD." http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706994/

Also in 2013, a study titled "Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent non-responsive celiac disease patients" (BMC Gastroenterol. 2013; 13: 40 – accessed at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3598839/) reported on "Patients with persistent symptoms and/or villous atrophy" who, "despite strict adherence to a gluten-free diet (GFD) have non-responsive celiac disease (NRCD). A subset of these patients has refractory celiac disease (RCD)...." The researchers postulated, "[S]ome NRCD patients may simply be reacting to gluten cross-contamination." The researchers developed a gluten-free diet consisting of only "whole, unprocessed foods, termed the Gluten Contamination Elimination Diet (GCED)," to test its effect on this group.

The results? "Prior to starting the GCED, 16 of the 17 compliant patients (94%) were symptomatic and all but 3 patients became asymptomatic during the GCED, giving a symptom response rate of 81% (13/16). Six patients met the criteria for RCD [Refractory Celiac Disease] prior to initiation of the GCED, with persistent symptoms and Marsh 3 histology. Five out of these 6 (83%) had full resolution of their symptoms after the GCED and no longer meet criteria for RCD."

This dramatic response indicates that very small levels of gluten may harm celiacs. The study authors concluded, "The GCED may be an effective therapeutic option for NRCD patients that have already failed a well-documented strict GFD and may aid in differentiating those patients reacting to trace amounts of gluten contamination from those who truly have RCD1. By avoiding an inaccurate diagnosis of RCD1, patients are able to avoid corticosteroids or immunotherapy. The expense and potential adverse health effects of this type of therapy make a dietary solution, aimed at the underlying etiology, particularly attractive."

The researchers recognized the need for more studies “to re-evaluate the actual incidence of RCD1 as it may currently be over-estimated.”

The GCED does not include processed foods, even if labeled gluten free.

K. Some OTC medication manufacturers are starting to label some products gluten free.

For examples of over-the-counter medications currently labeled gluten free, see http://celiacdisease.about.com/od/Gluten-Free-Medications/fl/Gluten-Free-Pain-Relievers.htm.

While such labels are helpful to and much appreciated by celiacs, these labels are not governed by the FDA Final Rule for food products and supplements. We applaud those drug companies who have taken the lead to voluntarily disclose whether or not they consider their products gluten free. However, celiacs have no remedy if any of these gluten free claims proves to be false. [For more on the issue of remedy, see Support for the requested proposed mandatory rule Section VIII, below.]

(There are reasons why simply applying the FDA’s Final Rule for foods and supplements to medications would not protect celiacs. As discussed in more detail below, celiacs admitted to hospitals and medical facilities generally cannot choose whether or not to take medications there, and they have no control over what medications will be available during a medical crisis. The stress and difficulty involved for the celiac patient of obtaining a voluntarily-labeledgluten-free-labeled choice (eg for contrast materials or pain relievers) in this situation is high. If the FDA’s Final Rule for foods and supplements were to be applied to medications, two other rules also would be needed to adequately protect celiacs: All prescription and over-the-counter medications would have to have at least one gluten-free-labeled version, and all hospitals and medical facilities would have to have voluntarily-labeled-gluten-free versions for all medications available. Such procedures would be difficult for drug manufacturers and medical facilities to administer and for the FDA to monitor.)

Support for the requested mandatory rule.

The requested proposed mandatory rule would, as more fully elaborated below in sections I

through XI:

- reduce reported gluten-related problems among celiacs,
- support celiacs’ rights as intended by the Americans With Disabilities Act
- minimize unhealthy consumer stress, increase consumer confidence, and likely increase consumer compliant use of drug products
- minimize uncertainties relating to individual drug products
- minimize uncertainties relating to drug products taken as a whole
- relieve consumers and pharmacists of the burden of solving problems that arise from uncertainties
- relieve manufacturers of the burdens imposed by uncertainties
- be cost-effective for manufacturers
- promote standardization that is easily achievable using good manufacturing practices
- rarely require labeling

- provide remedy for consumers should problems arise
- rarely require enforcement or remedy, as problems resulting from errors in implementing the rule are expected to be few
- provide both a single measurable standard (simplifying matters for manufacturers and the FDA) and a single common scale for celiacs with respect to their gluten consumption (simplifying matters for celiacs and their medical providers)
- use a standard that is both objective (free from bias) and testable (not speculative or anecdotal)
- promote transparency, increase positive patient-company relationships, reduce patientcompany conflicts and
- eliminate differences in how celiacs and drug manufacturers perceive how celiacs work to maximize their quality of life with respect to their use of medications and foods.

I. People with celiac disease are experiencing problems with prescriptions and over-the- counter medications that are not resolved by the risk analysis in the FDA's letter.

Celiac Support Group is a non-profit organization whose mission is "To maximize quality of life and health for those affected by Celiac Disease, Non-Celiac Gluten Sensitivity, Dermatitis Herpetiformis, and Gluten Ataxia." Among other efforts to realize this mission, Celiac Support Group published blog posts prior to Public Citizen's lawsuit to educate consumers who must avoid gluten on steps they can take to protect their health, given that current regulations and orders do not prohibit gluten in medications. These posts can be located at:

"Gluten In Drugs: Action Steps Needed" 12/31/14, at http://www.celiacsupportgroup.org/celiac-support-group-blog/gluten-in-drugs-actionsteps-needed

"Gluten In Drugs II: How to Find Out If Your Medications Are Gluten Free" 3/1/15, at http://www.celiacsupportgroup.org/celiac-support-group-blog/gluten-in-drugs-ii-how-tofind-out-if-your-medications-are-gluten-free

As the first post listed above notes, "We want the FDA to know that Celiac Support Group continues to hear from people who have experienced problems with prescription and/or over- the-counter drug products."

One recent example reported to us is that of two people who spent eight hours trying simply to find out what the starch source was in a generic of a prescribed medication (as pointed out in the FDA's 5/12/2015 letter, some starches may be made from both gluten and non-gluten sources). They could not get an answer to their question. They decided to not pay the much higher co-pay their medical insurer required for the brand name version of the drug. They did not fill the subscription.

According to its 5/12/2015 letter in response to Mr. Weber's petition and lawsuit, the FDA is receiving similar reports of problems. The letter states, for instance: "[Michael Weber's] petition and comments submitted to the docket impressed upon us that some individuals with celiac disease have difficulty seeking assurance that medications they take will not harm them."

The second post listed above shares that its author had had adverse gluten reactions from medications. Again, the FDA in its 5/12/2015 letter agrees: "Some commenters stated anecdotally that they have reacted to gluten present in drug products."

II. The proposed rule supports celiac disease patients' rights as intended by the Americans with Disabilities Act.

In the Americans with Disabilities Amendment Act of 2008, the United States Congress defined "major life activities" covered by the Americans With Disabilities Act, in order to "'provide a clear and comprehensive national mandate for the elimination of discrimination against individuals with disabilities' and provide broad coverage...." See http://www.eeoc.gov/laws/statutes/adaaa.cfm.

These "major life activities" were further defined, to include "caring for oneself," "eating," and "functions of the immune system, normal cell growth, digestive, bowel, bladder, neurological, brain, respiratory, circulatory, endocrine, and reproductive functions."

The Department of Justice later came to an agreement with a university regarding the university's mandatory food plan's need to accommodate students who have celiac disease. As the DOJ notes, "Some individuals with food allergies have a disability as defined by the ADA - particularly those with more significant or severe responses to certain foods. This would include individuals with celiac disease and others...." http://www.ada.gov/q&a_lesley_university.htm

When physicians prescribe drugs for patients, they may consider the drugs necessary for their patients' health. Looked at in this light, medications are like mandatory food plans, since such medications currently may contain both ingredients that physicians consider necessary for their patients' health and other contents that may negatively affect the functions of celiac disease patients' immune systems and their ability to care for themselves.

The requested proposed mandatory rule would support celiac patients' rights as intended by the Americans with Disabilities Act without burdening the pharmaceutical industry (see below).

III. The current situation creates stress for celiac individuals whenever they are prescribed medications, whenever their medications are changed, and whenever they experience side effects from their medications. Such stress is not conducive to health.

Several health-related websites acknowledge the recognized relationship between stress and health by emphasizing the importance of stress management. See, for example:
http://www.nimh.nih.gov/health/publications/stress/index.shtml
https://www.nlm.nih.gov/medlineplus/ency/article/001942.htm
http://www.mayoclinic.org/healthy-lifestyle/stress-management/in-depth/stress-symptoms/art-20050987
http://www.webmd.com/balance/stress-management/effects-of-stress-on-your-body
http://www.apa.org/helpcenter/stress.aspx

The current situation creates unhealthy stress for celiacs. Many must take multiple medications. They frequently arrive at the pharmacy to find that a new generic has replaced the prior one they had previously investigated. They live in dread of having to take a new medication at short notice.

The requested proposed mandatory rule would eliminate such unhealthy stresses. Instead, celiacs' confidence in drug products would increase. The rule therefore likely also would increase celiacs' compliant use of drug products.

IV. Given the current situation, the FDA's risk analysis in its 5/12/2015 letter and its plan to provide guidance to manufacturers are inadequate to relieve celiacs of concern or to protect them from actual danger, because the problem is not with the overall gluten risk in medications but rather with the uncertainty present regarding every individual drug product.

In the first post listed above, Celiac Support Group shared McNeil-PPC's statement that the company retracted a previous gluten-free claim: "Although we don't add gluten or gluten containing grains to our products, we cannot confirm that the product or any ingredients in TYLENOL® products are gluten free." This retraction resulted in Tylenol products being removed from the list of voluntarily-declared gluten-free drugs reported at http://glutenfreedrugs.com, but only after Celiac Support Group published the blog post, more than two months after McNeil-PPC's announcement.

It is difficult for celiacs to resolve their medication-related stresses by reducing their risk regarding any individual drug product. As described above, available generic products often change without notice.

Individual product ingredients also may change. The FDA has issued guidelines in this respect (see the 2014 "Guidance for Industry: CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports" at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM217043.pdf), but it is difficult for celiacs or their pharmacists to determine in a timely manner what manufacturers have to say about their products, and consumer choices may be limited.

One recent example that illustrates this difficulty was reported to us by a person whose medication (voluntarily claimed by the manufacturer to be gluten free) became no longer available at the pharmacy. The available substitute generic was not listed at http://glutenfreedrugs.com, but the person found another generic for the same medication that was both listed there and available at the pharmacy. When the person asked their doctor about this, he said he would not recommend the second product because it was stronger than the first and the contraindications for the two products differed.

V. The FDA's current stated intention to offer guidance to drug manufacturers increases rather than reduces uncertainties about gluten in medications.

The FDA letter reads, in this regard: "We intend to issue draft guidance for industry regarding gluten in drug products and associated labeling." The letter goes on to state: "If, in the future, despite these steps, FDA becomes aware of evidence that low levels of gluten in drug products are harming individuals with celiac disease, we will consider additional regulatory options."

No deadline was provided for when the FDA will act.

Uncertainty over not only what guidelines will be proposed but also when they will be proposed and how effective they might or might not be adds to the uncertainties and stresses currently experienced by affected celiac individuals, pharmacists, and manufacturers.

VI. When problems arise, it is unfair to place the burden of resolving them on concerned individual celiacs and pharmacists.

The undersigned believe that putting the burden of obtaining gluten free medications entirely on consumers rather than manufacturers places an unreasonable burden upon the 1.3% of Americans who have celiac disease as well as those with other gluten-related disorders who require gluten free medications to maintain or improve their health.

When problems arise, one option for individual celiacs to reduce their uncertainty and stress has been to test their medications for gluten. As the second blog post listed above notes, "The problem with this option is it uses some of your medication and depending on the amount and size of the medication, this could be a lot. In addition, some medications are specifically made to be 'crush proof '...AND test kits aren't cheap."

Using prescribed medications for testing purposes has the additional downside of reducing what remains for the

individual's use. Unlike food products, medications that are consumed "ahead of schedule" can't be replaced simply by going to the market for an early refill.

The requested proposed mandatory rule, unlike FDA future guidance, would reduce the burdens currently placed on individual celiacs and pharmacists due to the uncertainties and resulting stresses described above.

VII. The requested mandatory rule proposed above would reduce manufacturer uncertainties and promote standardization.

The FDA, in its 5/12/2015 letter, acknowledges that in the current situation a "careful manufacturer" "may hesitate to use the term gluten-free if it cannot be verified that the finished drug and all of its ingredients were produced in a way that reliably excluded adventitious contamination with gluten even at undetectable levels." The requested proposed mandatory rule would reduce manufacturer uncertainty over the allowed gluten content of their products not requiring labeling. This would reduce manufacturers' uncertainty over what to say to consumers about the gluten content of their products. In addition, the requested proposed mandatory rule would promote universal standardization.

The FDA states in its 5/12/15 letter: "Current good manufacturing practice requirements for drug products include a basic obligation that harmful or potentially harmful impurities be controlled."

The FDA currently does not consider gluten content in medications above 20 ppm gluten to be a "harmful or potentially harmful" impurity. The requested proposed rule would not require the FDA to make this determination, nor would it limit the amount or form of gluten allowed in medications. Rather, it would bring the labeling of medications in line with the FDA's Final Rule for labeling food products including supplements and with the finalized (currently proposed) FDA rule "Gluten-Free Labeling of Fermented or Hydrolyzed Foods". The difference is that the requested proposed mandatory rule for medications would require mandatory labeling gluten in certain instances, while the FDA's current and proposed rules foods relate to voluntarily labeling foods gluten-free. The effect for Celiacs would be the same, however: By reading labels, Celiacs could determine and be reassured that their total gluten consumption would not likely exceed an amount that would damage their villi. [See also Section IX below.]

Medication manufacturers, if given the specific maximum limits for gluten in products that would not require labeling under the requested proposed mandatory rule, can and would require their suppliers to use Good Manufacturing Practices (GMP) to deliver excipients of appropriate quality.

That this goal is achievable by suppliers is supported by the successes in the food industry in achieving less than 20 ppm gluten (indeed, often less than 5 ppm gluten) in gluten-free-labeled products, using Good Manufacturing Practices (GMP). Since the FDA's Final Rule for voluntarily labeling food products became effective in 2014, there have been few complaints to the FDA despite the explosion of products currently labeled gluten-free.

Because drug excipients may be created anywhere in the world, it is especially important that responsibility for product quality begins with the suppliers who provide medication manufacturers with the ingredients that manufacturers use in their products.

Accordingly, the requested proposed mandatory rule would reduce the burden on manufacturers, since suppliers' ability to achieve at or less than 20 ppm gluten for each of the manufacturers' product ingredients is achievable.

An additional benefit is that the requested proposed rule would reduce manufacturer uncertainties about the content of gluten in the final product. If all suppliers, using GMP, provide ingredients containing at or less than 20 ppm gluten and follow the conditions of the FDA final rule regarding ""Gluten-Free Labeling of Fermented or Hydrolyzed Foods," manufacturers' final products also should qualify as not requiring labeling under the requested proposed mandatory rule.

Reduced manufacturer uncertainties also would lower celiac consumer uncertainty and stress, because celiacs would no longer have to question manufacturers, and manufacturers no longer would feel compelled to provide vague and unhelpful responses, such as those reported in the second blog post listed above -- “Although the filler ingredients ‘shouldn’t’ contain gluten they are purchased from outside sources and not tested for gluten” and “People who have celiac disease should contact their doctor before taking this medicine.”

VIII. The good news in the FDA’s 5/12/2015 letter is that its risk analysis indicates that violations of the requested proposed rule are expected to be rare. The better news is that, in the rare instances in which violations of the requested proposed mandatory rule might occur, celiac consumers would have a remedy.

After the FDA’s 5/12/2015 letter was released, Celiac Support Group posted a third blog post on the topic of gluten in medications (at http://www.celiacsupportgroup.org/celiac-support-group-blog/gluten-in-medications-update). It concludes: “[E]very celiac must continue taking medications that are not regulated for gluten content. If any of us is unlucky enough to be sickened by them, the FDA currently provides no remedy.”

Mistakes can happen. When mistakes happen, it is important that they be corrected quickly. FDA rules and regulations provide procedures that ensure that corrections happen quickly. More importantly, FDA rules and regulations provide incentives to manufacturers to ensure that mistakes happen extremely infrequently if at all.

The requested proposed rule for medications would not burden the FDA. Since the FDA’s risk analysis considers the possibility of gluten being present in medications in excess of 20 ppm gluten to be rare, it follows that labeling required by the proposed rule also would be expected to be rare, and actual violations of the proposed rule would be expected to be even more rare.

IX. An advantage of the requested proposed mandatory rule above over FDA guidelines is that it provides a single, measurable standard for those creating ingestible products worldwide that are considered gluten free.

The proposed rule that requires the labeling of medications when the parts per million of gluten exceeds 20 would create the same standard as is used in the FDA Final Rule regarding the voluntary labeling of food products as gluten free. This would create a common scale to determine when ingestible products are considered appropriate for celiacs.

According to Capsule Connections at https://capsuleconnection.com/capsules, a ‘”00” [sized capsule] holds about 735 mg. “0” size holds about 500 mg. #1 holds about 400 mg. #2 about 300 mg. #3 about 200 mg.’

This means that if a single serving of a capsuled medication were to contain the maximum amount of gluten allowed in a 30 gm cookie labeled gluten free, the amount of gluten present in the medication would be between 40 and 150 times more concentrated than in the cookie. Such a medication might result in different effects for individual celiacs with individual immune system responses. This risk is increased given that celiacs may need to ingest multiple medications, multiple times per day, and/or for long periods of time.

Using a single, measurable standard of 20 ppm that would be used and applied to labeling rules for both medications and foods would simplify matters for manufacturers and the FDA and would reassure celiac consumers.

Since harm from gluten for celiacs is cumulative, a single measurable standard for gluten ingested both from food and medications also would allow the cumulative effects of gluten in individual celiacs’ diets to be more easily analyzed and addressed by medical providers.

X. An advantage of the requested proposed rule over FDA guidance is that any allegations or disputes involving gluten in medications would be resolved by a single testable standard, rather than by requiring investigation of anecdotal reports.

Testing, while not required under the requested proposed mandatory rule, is a relatively inexpensive way that manufacturers, celiacs, and if necessary the FDA could evaluate compliance and resolve disputes.

XI. In addition to differences in gluten concentration between a single serving of an oral medication and a single serving in a 30 gram cookie labeled gluten free, both containing the same *amount* of gluten, other differences between these "equal gluten amount" medication and cookie affect celiacs.

The FDA in several places in its 5/12/2015 letter compared the amount of gluten that could be legally present in a 30 gram gluten-free-labeled cookie and the amount possible in a single serving of an oral medication. The FDA in its 5/12/2015 letter states, "[W]ith the exception of exceedingly rare oral drug products to which wheat gluten or wheat flour has been added as an ingredient (which should be indicated in labeling), we are not aware of any oral drug product that contains more gluten than the amount potentially present in a 30 gram serving of food labeled gluten-free. Therefore, any celiac patient doing well on a gluten-free diet should not have to worry about the possible presence of hidden gluten in drug products. We would expect an individual with celiac disease who is not responding well to a gluten-free diet to consult with his or her physician about ways to further reduce gluten exposure. Such an effort might focus on the low milligram quantities of gluten potentially present in a daily gluten-free diet before any attention is paid to the much lower amounts potentially present in oral drug products and would further take into consideration the benefits and risks of any oral drug product identified as a potential source of gluten."

Beyond what was discussed above in Section IX, that the concentration of gluten in the single serving of the oral medication would be much higher than in a 30 gram gluten-free-labeled cookie, we wish to point out that there are several additional ways in which medications and cookies differ, from a celiac perspective.

The celiac patients who are not doing well on the gluten free diet may be more likely than other celiac patients to be experiencing problems that require medications and to be taking more medications than the other celiac patients. Some of these not-doing-well celiac patients may not be ingesting gluten from any easily identifiable source(s). As noted above, the GCED may reduce problems for these patients. Since the GCED does not include processed foods such as gluten-free-labeled cookies, it logically follows that it would be desirable that medications containing similar amounts of gluten also be avoided on the GCED. The success of the GCED in improving the health and quality of life for individuals with NRCD and/or RCD underscores the importance for these individuals of also minimizing gluten present in their medications.

Celiacs can choose whether to consume gluten free labeled cookies, can choose among gluten free labeled cookies, and can decide for themselves how many cookies they wish to consume and over what period of time. With prescribed medications, celiacs' actions are prescribed, leaving them with little or no choice as to whether, how much and how often to consume them.

Cookies can be obtained at leisure and after thorough investigation of ingredients and gluten risks. Prescription medications often must be obtained because of a medical crisis, when there may not be time or ability for consumers to adequately investigate and evaluate the medications' gluten free status prior to consumption.

Celiacs can choose to avoid cookies, whether or not labeled gluten free, without harming their health. For celiacs, cookies

are optional (and some celiacs don't eat gluten-free-labeled cookies at all, due to concerns about potential cumulative gluten exposure). Prescribed medications generally are not optional. Medications may be necessary for celiacs' health. Many medications must are taken for long periods, sometimes for life.

In the case of an adverse reaction, celiacs can discontinue eating a gluten-free-labeled cookie without causing harm. The same often cannot be said of a decision to discontinue a medication.

Celiacs can stock up on their favorite reliable gluten-free-labeled cookies. The same cannot be said of prescribed medications, for good and valid reasons.

On the other hand, and as noted above, celiacs in the current situation sometimes avoid ingesting both gluten-free-labeled cookies and prescribed medications. Certainly, this is not the result the FDA, manufacturers, medical providers or celiacs want.

Opposition to the requested proposed mandatory rule (Sections XII and XIII).

XII. We could find no written statements by the pharmaceutical or over-the-counter medications industries opposing the labeling of gluten above 20 ppm in drug products. Written statements by medication manufacturers in responses to FDA Docket 2011-N-0842 appear to support or be neutral regarding the proposed rule.

The FDA in its 5/12/2015 letter summarized objections to the FDA Docket 2011-N-0842 as follows:

"The International Pharmaceutical Excipients Council (IPEC)...stated that it supports FDA's interest in providing better options for individuals with celiac disease. IPEC noted that modified starches are often derived from sources other than wheat and that when excipients are derived from wheat, they are often highly processed so that gluten is removed or reduced below 20 ppm. IPEC cited ethanol USP as an example of an ingredient that may be produced through fermentation using wheat (among other sources). Ethanol produced in this manner is purified by distillation, which would effectively remove any gluten. IPEC noted that wheat gluten would be disclosed on drug labels in rare instances when it is added to a drug as an ingredient."

From this summary, it appears the IPEC would not oppose the requested proposed mandatory rule, as labeling would in most cases likely not be an issue because such labeling would in most cases not be necessary.

The Consumer Healthcare Products Association (CPHA) represents over-the-counter medicine manufacturers. Its response on March 20, 2012 to FDA Docket 2011-N-0842 is located at http://freepdfhosting.com/09c765f6cb.pdf.

In the FDA's 5/12/2015 letter, CPHA's position is summarized as follows:

'CHPA asserted that considering the "extremely low" levels of gluten in OTC drug products today, a ban on gluten-containing source ingredients would unnecessarily disrupt the supply chain and could limit the availability of important health care products. CHPA noted that inactive ingredients may be processed in ways that remove or reduce gluten to "an insignificant level." CHPA also asserted that except when wheat gluten is intentionally added, the amount of gluten in finished OTC drugs is "minute" especially compared to intake via the food supply. CHPA did not provide detailed exposure estimates or numerical values to support this. CHPA also noted that a complete ban on certain source materials may not guarantee a complete absence of gluten from drug products due to cross contamination.'

Since the proposed rule would not ban gluten-containing source ingredients and would require labeling only when gluten can be measured at above 20ppm gluten, it appears the CPHA, like the IPEC, likely would not contest the requested proposed mandatory rule.

The CHPA acknowledges the possibility of “cross contamination” in the creation of over-thecounter medicines. Presumably gluten, whether added intentionally or due to cross contamination, would in almost all cases be at the ‘insignificant’ or ‘minute’ levels the CHPA acknowledges may happen, and at these levels the requested proposed mandatory rule does not require labeling.

CHPA’s comparison of “gluten in finished OTC drugs” to “intake via the food supply” is irrelevant to the proposed rule. The purpose of mandatorily limiting the presence of gluten in prescription and over-the-counter medications and voluntarily limiting the presence of gluten in some processed foods is to protect people with celiac disease and other gluten-related disorders who do not participate and cannot participate in the gluten generally available in the food supply.

The CPHA acknowledged that “It is unclear if” gluten-grain product derivatives processed to remove gluten “present risks to persons who have celiac disease.” The undersigned agree. It is one additional reason that the requested proposed mandatory rule uses the same limit in ppm gluten for medications as is allowed in foods under the FDA’s Final Rule on voluntary labeling of gluten in foods.

The need for persons with celiac disease and other gluten-related disorders for medications that are reliably gluten free in all circumstances where medications for health are required, sometimes at extremely short notice, is the reason that the proposed rule is requested to be mandatory rather than voluntary.

XIII. Because the proposed rule does not require manufacturers to remove all gluten from medications and in addition does not require pharmaceutical companies to be explicit about their excipients, and because the proposed rule would not result in excessive labeling, the proposed rule should not cause manufacturers or the FDA to object on these grounds.

In its 5/12/2015 letter, the FDA states, “There are risks associated with excessive labeling of drug products as containing wheat-derived ingredients, namely that patients would forego important medications if they were labeled as containing wheat or gluten despite containing only extremely low levels of gluten, not likely to harm a typical individual with celiac disease.”

As described above, there also are risks associated with not labeling drug products as regards gluten content, especially if patients sometimes forego important medications when they cannot get reassurance that the drugs in question will not harm them. Certainly celiacs, doctors, manufacturers and the FDA do not support this unintended result.

The requested proposed mandatory rule would both protect celiacs and result in “infrequent labeling” (not “excessive labeling”).

Elsewhere in its 5/12/2015 letter, the FDA states that there may be some problems with appropriate testing: “We recognize that there are challenges associated with analytical testing of finished drug products for gluten and would welcome additional research in this area.”

Testing would not required under the requested proposed mandatory rule for labeling purposes. If testing is required to resolve a dispute involving the requested proposed mandatory rule, the best appropriate test available at the time of a dispute is the one that logically would be used.

Conclusion

The requested proposed mandatory rule will protect celiacs and increase their ability to maximize their quality of life without imposing burdens on medication manufacturers or the FDA.

C. Environmental Impact

The undersigned request categorical exclusion from an environmental assessment in this petition, as per the following FDA language: “(A) Claim for categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.”

D.Economic Impact

Because information in this section is to be submitted only when requested by the Commissioner following review of the petition, this section remains blank.

E. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Signatures (8) As individual United States Citizens:

Names of Petitioners: Meghan O’Hara, Robert Vogel, Karen Bazlen, Diane Craig, Jessica Denning, Laurie Willson, Melanie Weir, Susan Larock